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EXAMINER
HA, JULIE

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/529,203	BAUER ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10,12-14,16-18,29,30,32,33,35-38,40 and 42-57* is/are pending in the application.

4a) Of the above claim(s) *50-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10,12-14,16-18,29,30,32,33,35-38,40,42-49 and 55-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *April 21, 2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response after Non-final filed on April 21, 2010 is acknowledged. Claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-38, 40, 42-57 are pending in this application. Claims 50-54 remain withdrawn from further consideration, as being drawn to nonelected invention. Claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-38, 40, 42-49 and 55-57 are examined on the merits in this office action.

1. This application contains claims 50-54 drawn to an invention nonelected with traverse in the reply filed on May 21, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn Objections

2. The objection to the figures is hereby withdrawn in view of Applicant's amendment to the drawings and specification.

Maintained Rejection

35 U.S.C. 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-37, 43-49 and 55-57 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gefter et al (US Patent No. 6,180,608) in view of Bauer et al (PG Pub 2002/039996).

7. Gefter et al teach pharmaceutical compositions comprising a stable water-insoluble complex composed of a peptidic compound, preferably a pharmaceutically active peptidic compound, and a carrier macromolecule that allows for sustained delivery of the peptidic compound in vivo upon administration of the complex. The reference further teaches that the complex can permit continuous delivery of a

pharmaceutically active peptidic compound to a subject for prolonged periods of time, e.g., one month, two months, three months and the like (see column 1, lines 43-52 and column 6, lines 12-13). Furthermore, the reference teaches that the complex is formed by combining the peptidic compound and the carrier macromolecule under conditions such that a substantially water-insoluble complex is formed, e.g., aqueous solutions of the peptidic compound and carrier macromolecule are mixed until the complex precipitates. The complex may be in the form of a solid (e.g., a paste, granules, a powder or a lyophilisate)…can be pulverized finely enough to form stable liquid suspensions or semi-solid dispersions (see column 1, lines 57-65). This reads on claim 33 and claim 36 in part. The reference further teaches that the peptidic compound of the water-insoluble complex is an LHRH analog, and LHRH antagonist (see column 1, lines 66-67 and column 2, line 1). Furthermore, the reference teaches that the complex is suitable for sterilization, such as by gamma irradiation or electron beam irradiation, prior to administration *in vivo* (see column 2, lines 3-5). This reads on claims 36 and 37. Further, the reference teaches a method for treating a subject for a condition (prostate cancer) treatable with an LHRH analog by administering to the subject an LHRH-analog-containing composition (see column 2, lines 6-11). This reads on claims 48-49. The LHRH analogs are LHRH antagonists, and include antide, Cetrorelix and the like (see column 4. lines 6-27). The reference further discloses that multivalent cationic peptidic compound and multivalent anionic peptidic compound refer to peptidic compound comprising a multiplicity of positive or negative charges (see column 3, lines 46-49). Furthermore, the reference teaches that the pharmaceutical formulations

comprise additional pharmaceutically acceptable carriers and/or excipients…the carrier is suitable for intravenous, intramuscular, subcutaneous or parenteral administration (e.g., by injection) (see column 7, lines 65-67 and column 8, lines 1-7). This reads on claim 43. The reference further teaches that a non-limiting range of an LHRH analog is 0.01 mg to 10 mg/kg (see column 10. lines37-38) and Examples 2-4 discloses 25 mg of peptidic compound dissolved in water (Example 2), 50 mg of peptidic compound dissolved in mannitol and carboxymethylcellulose (Example 3) and 25 mg of peptidic compound dissolved in water and added to sodium alginate (Example 4). This reads on claims 16-18. The reference further teaches that the reconstitution vehicle to be used in clinical studies is 0.9% sodium chloride (see Example 14). This reads on claims 12-14 and 27. The difference between the reference and the instant claims are that the reference does not teach D-63153, and additionally pharmaceutically active ionic peptide compound and differing NaCl concentrations of 0.05 to 0.5% (weight/volume) and 0.1 to 0.2%.

8. However, Bauer et al disclose a pharmaceutical administration forms suitable for parenteral administration, which contains peptides prone to aggregation in the form of their acetate, gluconate, glucuronate, lactate, citrate, ascorbate, benzoate, or phosphate salts in dissolved or dispersed form (see abstract). Furthermore, the reference discloses that the pharmaceutical administration forms can be present in dissolved or dispersed form in water or in aqueous solvent mixtures (see paragraph [0012]). Additionally, the reference discloses that the peptides employed are LHRH antagonists antide, A-75998, ganirelix and Nal-Glu antagonist, but in particular cetrorelix, antarelix and the

antagonists according to the U.S. Patent # 5942493 and DE 19911771.3. (see paragraph [0014] and US Patent No. 7,005,418, column 3, lines 53-58). D-63153 is an antagonist disclosed in DE 19911771.3. Furthermore, the reference discloses that preparation of sterile solutions of LHRH antagonist for parenteral administration is by means of filtration, especially at high concentration (see paragraph [0009]). Additionally, the reference discloses that the administration of pharmaceutically active peptides is the parenteral pharmaceutical form…in the form of reconstituted lyophilisates of soluble peptide salts and to microparticles, microcapsules or implants (see paragraph [0010]). Furthermore, the reference discloses that area of use of the preparations is in the prevention and therapy of all sex hormone-dependent conditions and diseases, which can be influenced by LHRH agonist and antagonists…benign prostate hyperplasia, carcinoma of the prostate, precocious puberty, hirsutism, endometrial hyperplasia, uterine myomatosis, breast cancer, etc (see paragraphs [0020] and [0021] and claims 16 and 17). Furthermore, the reference discloses rat animal experiment (see paragraph [0041] and Tables 8a, 8b and 9). Please note that the reference discloses the disorders that are claimed in claims 50-53 of instant application.

9. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Gefter et al and Bauer et al because both prior arts teach pharmaceutical gel formulation incorporating GnRH antagonist. There is a motivation to substitute D-63153 for other GnRH antagonists since they are all recognized GnRH antagonist and one would expect the same activity. There is a reasonable expectation of success to substitute D-63153 for other GnRH antagonist, since both prior arts

disclose Antide and Cetrorelix as examples of GnRH antagonists that can be formulated into composition in an aqueous solvent. Further, there is a reasonable expectation of success since 0.9% sodium chloride is used to reconstitute for clinical studies (see Example 14 of patent '608) and sustained delivery formulation for administering pharmaceutically active peptides *in vivo* continuously for prolonged time periods are achieved by patent '608. The references are silent as to the range of NaCl concentrations.

10. However, the MPEP states the following: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. *"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."* *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)* (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.*"); *In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969)* (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be

unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Therefore, there is a reasonable expectation of success to optimize the NaCl concentration, since "*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."* One of ordinary skill in the art would have been motivated to optimize the NaCl range with for the expected benefit of at least increasing the clinical utility of the pharmaceutical preparation.

11. Furthermore, the MPEP states the following: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the

aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....Appellant argues... hindsight reconstruction or at best,... obvious to try'.... We agree with appellant."). Therefore, there is a reasonable expectation of success to add in another pharmaceutically active ionic peptide compound in a pharmaceutical gel preparation comprising D-63153, since the above mentioned compounds (such as cetrorelix) are all GnRH antagonist that are used for the same purpose, thus addition of another GnRH antagonist would at least have an additive effect.

Response to Applicant's Arguments

12. Applicant argues that "Gefter et al disclose a pharmaceutical composition comprising a water-insoluble complex composed of a peptidic compound and a macromolecule carrier that allows for sustained release of the peptidic compound in vivo upon administration of the complex. The peptidic compound of Gefter et al comprises peptides, polypeptides and proteins. In Gefter et al, the carrier

macromolecule comprises cationic carrier macromolecule like poly-L-lysine and other polymers of basic amino acids or anionic carrier macromolecule like polyalcohol derivatives. The current invention does not comprise a carrier macromolecule and does not use such carrier macromolecule." Applicant argues that "Although Applicant agree that the "comprising" terminology permits the inclusion of additional components, it is noted that the form of the product is important...In Gefter et al the carrier macromolecule is necessary to permit formation of a sustained release complex where in contrast the claimed invention the sustained release complex is formed after reconstitution of a lyophilized form D-63153 or a pharmaceutically active salt thereof." Applicant argues that "Gefter et al use a 0.9% sodium chloride in Example 14 as a reconstitution vehicle to reconstitute the complex PPI-149-CMC, consisting of the peptidic compound PPI-149 and macromolecule carboxymethylcellulose."

Applicant further argues that "Gefter et al use a 0.9% sodium chloride in Example 14 as a reconstitution vehicle to reconstitute the complex PPI-149-CMC, consisting of the peptidic compound PPI-149 and the macromolecule carboxymethylcellulose, wherein the complex PPI-149-CMC is *already a sustained delivery complex*. This is not what is claimed. The claim relate to reconstitution of the lyophilized form of D-63165."

Further, Applicant argues that "Bauer et al discloses that peptide have a nature prone to uncontrolled aggregation and that the peptides if administered lead to a concentration-dependent lowering of the bioavailability form the peptide concentration. Bauer et al therefore disclose that the addition of a free acid to the easily soluble peptide salt prevents that peptide salts prone to aggregation." Applicant argues that

"Bauer et al does not actually disclose or suggest D-63153. U.S. Patent No. 5,942,493 and DE 19911771.3 references disclose a large number of peptides, one of which is D-63153. However, Bauer et al or these references fail to provide any specific motivation to select D-63153 for use as presently claimed." Furthermore, Applicant argues that "Bauer et al disclose a pharmaceutical administration form which contains peptides prone to aggregation. Bauer et al provide a teaching to avoid aggregation of the peptides whereas the presently claimed invention is a sustained release formulation and consequently involves the aggregation of peptides by reconstitution of lyophilized peptide salts with inorganic salts or acetic acid salts. Thus, the mechanism by which the claimed invention is achieved as compared to the cited are at direct odds and are incompatible. The Examiner makes no attempt to address this deficiency Bauer et al and the incompatibility of the disclosures of Bauer et al and Gefter et al."

Applicant further argues that "Examples 1 to 7 describe numerous examples where D-63153 is reconstituted in 0.1% to 0.2% sodium chloride. In Example 2, D-63153 reconstituted in 0.1% sodium chloride is shown to retain absolute bioavailability…Examples 4-7 provide various viscosity studies with D-63153 reconstituted in 0.1% to 0.2% sodium chloride, with Example 7 illustrating the clear advantages obtained by reconstitution of D-63153 in sodium chloride." Applicant argues that "Example 7 illustrating the clear advantage obtained by reconstitution of D-63153 in sodium chloride. Gefter et al and Bauer et al do not disclose or suggest these illustrated effects, and as such, it cannot be fairly considered that such an effect would be expected."

13. Applicant's arguments have been fully considered but have not been found persuasive. Applicant reiterates most of similar arguments previously filed. Gefter et al teach the GnRH (LHRH) antagonist such antide and cetrorelix and a carrier molecule for sustained release *in vivo*. It is reiterated that, in regards to Applicant's argument that instant invention "does not comprise a carrier macromolecule and does not use such carrier macromolecule", Applicant is reminded that the claim recites the transitional phrase "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps (see MPEP 2111.03). The MPEP states that The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., > *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) ("like the term comprising,' the terms containing' and mixture' are open-ended.").< *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in

major amounts"). >*In Gillette Co. v. Energizer Holdings Inc.*, 405 F.3d 1367, 1371-73, 74 USPQ2d 1586, 1589-91 (Fed. Cir. 2005), the court held that a claim to "a safety razor blade unit comprising a guard, a cap, and a group of first, second, and third blades" encompasses razors with more than three blades because the transitional phrase "comprising" in the preamble and the phrase "group of" are presumptively open-ended. "The word comprising' transitioning from the preamble to the body signals that the entire claim is presumptively open-ended." Id. Therefore, other elements may be included in the claimed language. Further, Gefter reference teaches the reconstitution of the GnRH antagonist in 0.9% NaCl for clinical utility. Since the sustained release form of PPI-149 is being reconstituted in the same NaCl solution, this meets the limitation of the claims. Additionally, the claim recites, "about 0.5% sodium chloride (weight/volume)". The term "about" can be broadly interpreted to also include "0.9% sodium chloride". Gefter et al teach that GnRH (LHRH) antagonist such antide and cetrorelix and a carrier molecule that is reconstituted in sodium chloride solution for pharmaceutical use. The reconstituted GnRH antagonist complex in sodium chloride would necessarily have the same function and activity, since the GnRH antagonist complex has sustained release activity. The claims do not recite that there is no other components involved in the pharmaceutically active salt thereof, and that sustained release activity is present only when the lyophilized form is reconstituted in NaCl solution. Gefter also teaches lyophilized GnRH composition that is reconstituted in NaCl solution for clinical use. Furthermore, claims 44-47 recite that "pharmaceutical preparation displays a sustained

pharmaceutical activity". The pharmaceutical composition of Gefter et al show sustained release activity.

Bauer reference teaches that pharmaceutically active decapeptides (cetrorelix) in the form of their pharmaceutically acceptable, non-toxic acid addition salts such as hydrochlorides…acetates, citrates…etc (see paragraph [0002]). Further, Bauer discloses pharmaceutical administration forms suitable for parenteral administration, which contains peptides prone to aggregation in dissolved or dispersed form and the peptides are present in the form of their acetate salts. Further, Bauer discloses that the administration of pharmaceutically active peptides is the parenteral pharmaceutical form…in the form of reconstituted lyophilisates of soluble peptide salts and to microparticles, microcapsules or implants. The Bauer reference teaches the LHRH antagonists antide, A-75998, ganirelix and Nal-Glu antagonist, but in particular cetrorelix, antarelix and the antagonists according to the U.S. Patent # 5942493 and DE 19911771.3 in dissolved form, for parenteral administration. Bauer reference was utilized to show that many different GnRH (LHRH) antagonists are well known in the art. The fact that Bauer teaches that the peptides have a nature prone to uncontrolled aggregation has no bearing on the rejection. This is a peptide characteristic. Bauer discloses different GnRH (LHRH) antagonists and their uses of the preparations in the prevention and therapy of all sex hormone-dependent conditions and diseases. Furthermore, both prior arts teach pharmaceutical gel formulation incorporating GnRH antagonist. Applicant has not shown that substitution of one GnRH antagonist for another would not work.

Additionally, the instant claims recite, "a mixture of D-63153 in lyophilized form and an aqueous solution of an inorganic or acetic acid at a concentration of from 0.05% to 0.5%." A solubilized peptide can be in a pharmaceutical gel preparation. Gefter reference teaches GnRH antagonist in NaCl solution, and Bauer et al disclose LHRH antagonists antide, A-75998, ganirelix and Nal-Glu antagonist, but in particular cetrorelix, antarelix and the antagonists according to the U.S. Patent # 5942493 and DE 19911771.3 in solubilized form for parenteral administration.

There is a motivation to substitute D-63153 for other GnRH antagonists since they are all recognized GnRH antagonist and one would expect the same activity. In regards to Applicant's argument that "Bauer et al does not actually disclose or suggest D-63153. U.S. Patent No. 5,942,493 and DE 19911771.3 references disclose a large number of peptides, one of which is D-63153. However, Bauer et al or these references fail to provide any specific motivation to select D-63153 for use as presently claimed." As indicated above in the body of the rejection, U.S. Patent No. 7,005,418 indicates that the antagonist can also be the LHRH antagonist D-63153 as described in the German Patent Application No. 199 11 771.3 (see column 3, lines 53-57). A large number of peptide antagonists is provided and known in the art. The MPEP states the following: "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958) (The mere fact that components are claimed as members of a Markush group cannot be relied upon to

establish the equivalency of these components. However, an applicant's expressed recognition of an art-recognized or obvious equivalent may be used to refute an argument that such equivalency does not exit.) ** *Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980) (The mere fact that phthalocyanine and selenium function as equivalent photoconductors in the claimed environment was not sufficient to establish that one would have been obvious over the other. However, there was evidence that both phthalocyanine and selenium were known photoconductors in the art of electrophotography. "This, in our view, presents strong evidence of obviousness in substituting one for the other in an electrophotographic environment as a photoconductor." 209 USPQ at 759.)" See MPEP 2144.06.

Furthermore, the KSR states the following: It has been held that under KSR that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in KSR, When there is motivation "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727,_,82 USPQ2d 1385, 1397 (2007).

The "problem" facing those in the art was developing a sustained release formulation comprising GnRH antagonist, and there were a limited number of peptide antagonists and methodologies available to do so, for example Cetrorelix, teverelix,

abarelix, ganirelix, azaline B, antide, detirelix, ramorelix, degarelix, D-63153, Nal-Glu, antarelix etc. Gefter teaches GnRH antagonist reconstituted in 0.9% NaCl for clinical studies. The skilled artisan would have had reason to try any GnRH antagonist and methodologies with the reasonable expectation that at least one would be successful. The GnRH antagonists are well known in the art. Thus, pharmaceutical formulation comprising any one of GnRH antagonist in an aqueous solution of inorganic salt is a "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

Additionally, since the claims do not further limit the structural attributes of the pharmaceutical gel preparation, and since the prior arts teach the peptides having these limitations in pharmaceutical gel preparations, the process of making (mechanism of how the product is achieved) still would not limit the structural attributes. The pharmaceutical preparation of the combined prior art comprise the GnRH/LHRH antagonist and the NaCl solution. Therefore, one would be motivated to optimize the pharmaceutical gel preparation by optimizing the peptide concentration and NaCl concentration. Therefore, there is a reasonable expectation of success to optimize the NaCl concentration, since "*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."* One of ordinary skill in the art would have been motivated to optimize the NaCl range with for the expected benefit of at least increasing the clinical utility of the pharmaceutical preparation.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In regards to Applicant's argument "Examples 1 to 7 describe numerous examples where D-63153 is reconstituted in 0.1% to 0.2% sodium chloride…with Example 7 that illustrating the clear advantages obtained by reconstitution of D-63153 in sodium chloride." Gefter et al teach the GnRH antagonist reconstituted in 0.9% NaCl for clinical use. Applicant has not shown any data comparison of differing NaCl concentrations and its effect on the blood plasma, the viscosity and so on. The only data shown are for those in 0.1% NaCl concentration. The data cannot be compared, since the data only shows using 0.1% and 0.2% NaCl. It is not known what the viscosity would be at 0.9% NaCl. It cannot be determined if there is any advantage or beneficial effect or unexpected results, since the only data shown is for 0.1% NaCl and 0.2% NaCl and not for different NaCl concentrations. No data is known for 0.3%, 0.4% and so on. The viscosity can be the same for 0.9% NaCl as is with 0.1 or 0.2% NaCl. Additionally, the MPEP states the following: "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPA 716, 718 (CCPA

1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). See MPEP 2145 I.

Therefore, the prior arts are obvious over claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-37, 43-49 and 55-57.

14. Claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-38, 40, 42-49 and 55-57 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gefter et al (US Patent No. 6,180,608) in view of Bauer et al (US 2002/039996) as applied to claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-37, 43-49 and 55-57 above, in further view of Engel et al (US Patent No. 5,663,145).

15. The teachings of Gefter et al and Bauer et al are described, *supra*. The difference between the references and the instant claims is that the references do not teach a kit.

16. However, Engel et al teach substances available for treating hormone-dependent malignant diseases (see column 1, lines 6-7). Engel teaches that Cetrorelix (INN) is an antagonist for LHRH (see column 1, line 15). Engel teaches that in clinical trials, a daily dose of 10 mg showed a complete suppression of the hormone concentration to castration level (see column 1, lines 20-22). Additionally, Engel teaches the dosage regimen of the pharmaceutical composition: an initial dose with the amount of 1-60 mg in a lyophilisate ampoule or several lyophilisate ampoules; lyophilisate ampoules in a

slow-release form with a rate of delivery of 0.1-10 mg/day for the whole period of treatment; or lyophilisate ampoules which contain the amount of active substance, which is not in a slow-release form, in an amount of 0.1-10 mg (see column 1, lines 42-54). The reference further teaches the aseptic procedures and lyophilizing the Cetrorelix solution (see column 2, lines 24-40). Furthermore, the reference teaches a kit comprising LHRH antagonist, Cetrorelix (see claims 1-3) and the method of treating a hormone-dependent condition (prostate cancer) comprising administering LHRH antagonist (Cetrorelix) (see claims 7 and 13).

17. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Gefter and Bauer and Engel because the prior arts teach the pharmaceutical formulation of GnRH antagonists in liquid form. All three prior arts teach the method of treating a hormone-dependent condition (prostate cancer) by administering a pharmaceutical composition of Cetrorelix. Bauer further discloses D-63153 as one of the peptides employed (see paragraph [0014] and see US Patent No. 7,005,418, column 3, lines 53-58). One of ordinary skill in the art would be motivated to substitute D-63153 for other GnRH antagonists since they are all recognized GnRH antagonist according to the prior arts, and thus, one would expect the same activity. There is a reasonable expectation of success since the Bauer and Engel teach the use of the formulation for the treatment of hormone-dependent disorder, specifically prostate cancer. Furthermore, there is a reasonable expectation of success since GnRH antagonists have similar properties, such as solubility, and are used to treat the same disorder.

Response to Applicant's Arguments

18. Applicant argues that "a combination of the teaching of Gefter et al, Bauer et al, and Engel et al would not directly lead a person skilled in the art to the subject matter of the aforementioned kit claims neither to any other amended claim as proposed herein for the reasons already provided above." Applicant further argues that "Engel et al disclose a dosage regimen of the pharmaceutical composition in which lyophilisate ampoules are in the form of an acetate and it is not intended to bring it in a slow release form according to the invention or are already in a slow release form and such slow release form is an embonate salt or the soluble peptide salt is embedded in microparticles. Such slow release form is not the starting form of the present invention."

19. Applicant's arguments have been considered but have not been found persuasive because all three cited prior arts teach the pharmaceutical formulation of GnRH antagonists in liquid form. Furthermore, Gefter et al teaches that the GnRH (LHRH) antagonist is in solid form (lyophilisate) and reconstituted in NaCl for clinical purposes. All three prior arts teach the method of treating a hormone-dependent condition (prostate cancer) by administering a pharmaceutical composition of Cetrorelix. Gefter et al teach the GnRH (LHRH) antagonist such antide and cetrorelix and a carrier molecule for sustained release *in vivo*. Further, Gefter reference teaches the reconstitution of the GnRH antagonist in 0.9% NaCl for clinical utility. Since the sustained release form of PPI-149 is being reconstituted in the same NaCl solution, this meets the limitation of the claims. Additionally, the claim recites, "about 0.5% sodium

chloride (weight/volume)". The term "about" can be broadly interpreted to also include "0.9% sodium chloride". Gefter et al teach that GnRH (LHRH) antagonist such antide and cetrorelix and a carrier molecule that is reconstituted in sodium chloride solution for pharmaceutical use. The reconstituted GnRH antagonist complex in sodium chloride would necessarily have the same function and activity, since the GnRH antagonist complex has sustained release activity. The claims do not recite that there is no other components involved in the pharmaceutically active salt thereof, and that sustained release activity is present only when the lyophilized form is reconstituted in NaCl solution. Gefter also teaches a GnRH composition that is reconstituted in NaCl solution for clinical use. Furthermore, claims 44-47 recite that "pharmaceutical preparation displays a sustained pharmaceutical activity". The pharmaceutical composition of Gefter et al show sustained release activity. Since the sustained release form of PPI-149 is being reconstituted in the same NaCl solution, one would be motivated to try reconstitution other GnRH/LHRH antagonist in the same aqueous solution. Gefter et al teach the GnRH antagonist reconstituted in 0.9% NaCl for clinical use. Applicant has not shown any data comparison of differing NaCl concentrations and its effect on the blood plasma, the viscosity and so on. The only data shown are for those in 0.1% and 0.2% NaCl concentration. The data cannot be compared, since the data only shows using 0.1% NaCl only. It cannot be determined if there is any advantage or beneficial effect or unexpected results, since the only data shown is for 0.1% NaCl and not for different NaCl concentrations. The data cannot be compared, since the data only shows using 0.1% and 0.2% NaCl. It is not known what the viscosity would be at 0.9% NaCl. It

cannot be determined if there is any advantage or beneficial effect or unexpected results, since the only data shown is for 0.1% NaCl and 0.2% NaCl and not for different NaCl concentrations. No data is known for 0.3%, 0.4% and so on. The viscosity can be the same for 0.9% NaCl as is with 0.1 or 0.2% NaCl. Additionally, the MPEP states the following: "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPA 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). See MPEP 2145 I.

Bauer reference teaches that pharmaceutically active decapeptides (cetrorelix) in the form of their pharmaceutically acceptable, non-toxic acid addition salts such as hydrochlorides…acetates, citrates…etc (see paragraph [0002]). Further, Bauer discloses pharmaceutical administration forms suitable for parenteral administration, which contains peptides prone to aggregation in dissolved or dispersed form and the peptides are present in the form of their acetate salts. Further, Bauer discloses that the administration of pharmaceutically active peptides is the parenteral pharmaceutical form…in the form of reconstituted lyophilisates of soluble peptide salts and to microparticles, microcapsules or implants. The Bauer reference teaches the LHRH antagonists antide, A-75998, ganirelix and Nal-Glu antagonist, but in particular cetrorelix, antarelix and the antagonists according to the U.S. Patent # 5942493 and DE 19911771.3 in dissolved form, for parenteral administration. Bauer reference was utilized to show that many different GnRH (LHRH) antagonists are well known in the art.

The fact that Bauer teaches that the peptides have a nature prone to uncontrolled aggregation has no bearing on the rejection. This is a peptide characteristic. Bauer discloses different GnRH (LHRH) antagonists and their uses of the preparations in the prevention and therapy of all sex hormone-dependent conditions and diseases. Furthermore, both prior arts teach pharmaceutical gel formulation incorporating GnRH antagonist. Applicant has not shown that substitution of one GnRH antagonist for another would not work. One of ordinary skill in the art would be motivated to substitute D-63153 for other GnRH antagonists since they are all recognized GnRH antagonist according to the prior arts, and thus, one would expect the same activity.

Engel reference was utilized to show that GnRH compositions are provided in kits. Since Gefter teaches that the composition is reconstituted in NaCl solution for clinical use, it would be obvious to one of ordinary skill in the art to provide the pharmaceutical composition in a kit for medical use. There is a reasonable expectation of success since the Bauer and Engel teach the use of the formulation for the treatment of hormone-dependent disorder, specifically prostate cancer. Furthermore, there is a reasonable expectation of success since GnRH antagonists have similar properties, such as solubility, and are used to treat the same disorders. All three prior arts teach the method of treating a hormone-dependent condition (prostate cancer) by administering a pharmaceutical composition of Cetrorelix. The instant claims do not further limit the structural attributes of the pharmaceutical gel preparation, and Engel et al teach the dosage regimen: an initial dose with the amount of 1-60 mg in a lyophilisate ampoule or several lyophilisate ampoules; lyophilisate ampoules in a slow-release form with a rate

of delivery of 0.1-10 mg/day for the whole period of treatment; or lyophilisate ampoules which contain the amount of active substance, which is not in a slow-release form, in an amount of 0.1-10 mg (see column 1, lines 42-54) and furthermore, teach a kit comprising the LHRH antagonist. Engel et al teach the kit comprising dosage in lyophilisate ampoules (see claims 4-5) and in slow-releasing formulation (see claim 6). Since the Gefter teaches that for clinical use, NaCl is used to reconstitute the lyophilisate, it would be obvious to one of ordinary skill in the art to include a NaCl solution in the kit for reconstitution purposes.

There is a reasonable expectation of success since the Gefter, Bauer and Engel teach the use of the formulation for the treatment of hormone-dependent disorder, specifically prostate cancer. Furthermore, there is a reasonable expectation of success since GnRH/LHRH antagonists have similar properties, such as solubility, and are used to treat the same disorders. Therefore, the prior arts combined meets the limitations of claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-38, 40, 42-49 and 55-57.

Conclusion

20. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). No claim is allowed.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654